

Best Available Copy

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 2001-038170

(43)Date of publication of application : 13.02.2001

(51)Int.Cl.

B01D 69/08

B01D 71/44

B01D 71/68

(21)Application number : 11-219912

(71)Applicant : TOYOBO CO LTD

(22)Date of filing : 03.08.1999

(72)Inventor : KYO MOTOKI
KATO NORIAKI
TSUCHIYA TOSHIYUKI

(54) HOLLOW FIBER MEMBRANE

(57)Abstract:

PROBLEM TO BE SOLVED: To provide hollow fiber membrane which is capable of reducing such risk that anaphylaxis response or pyrexia during dialysis is caused, and also has excellent properties with respect to assembling of the membrane hollow fibers into a membrane module.

SOLUTION: This hollow fiber membrane substantially consists of a polysulfone-based polymer and polyvinylpyrrolidone, wherein the correlation of the polyvinylpyrrolidone content (Ci) in the inner surface of the membrane with the polyvinylpyrrolidone content (Co) in the outer surface of the membrane and the average polyvinylpyrrolidone content (Cave) inside the membrane, is represented by the following relational expressions: $C_i \geq C_o \times 3$; and $C_i \geq C_{ave} \times 2$.

LEGAL STATUS

[Date of request for examination]

24.04.2003

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

Copyright (C); 1998,2003 Japan Patent Office

* NOTICES *

JPO and NCIP are not responsible for any damages caused by the use of this translation.

1.This document has been translated by computer. So the translation may not reflect the original precisely.

2.*** shows the word which can not be translated.

3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]

[Claim 1] The hollow fiber which is film which consists of a polysulfone system polymer and a polyvinyl pyrrolidone substantially, and is characterized by expressing the relation of the polyvinyl-pyrrolidone content (Ci) of a film internal surface, the polyvinyl-pyrrolidone content (Co) of a film outside surface, and the average polyvinyl-pyrrolidone content (Cave) in the film with a bottom type.

$Ci \geq Cox3$ and $Ci \geq Cavex2$ -- [Claim 2] The hollow fiber according to claim 1 whose membranous endotoxin adsorption capacity force is two or more 2000 EU/m.

[Claim 3] The hole density of a film outside surface is 25%. Hollow fiber according to claim 1 or 2 which it is above.

[Claim 4] The hollow fiber according to claim 1 to 4 in which it obtains and deals by washing this hollow fiber 30 seconds or more in hot water 80 degrees C or more after water 40 degrees C or more washes 1 minute or more in a spinning process.

[Translation done.]

* NOTICES *

JPO and NCIP are not responsible for any damages caused by the use of this translation.

- 1.This document has been translated by computer. So the translation may not reflect the original precisely.
- 2.**** shows the word which can not be translated.
- 3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to a new hollow fiber. There is little generating of an anaphylactic reaction, it is the film used for the therapy of renal failure etc. in detail, since mixing of endotoxin can be prevented by adsorption, safety is high, and it is related with the blood purification film excellent in module-assembly nature.

[0002]

[Description of the Prior Art] Most uses a polyvinyl pyrrolidone (PVP) for the blood purification film which uses a polysulfone system polymer as a raw material as a membranous hydrophilization agent. Since hydrophilization of the film will be carried out if PVP is used, adsorption of the plasma protein to a film surface can be controlled, a membranous fractionation property improves, and the engine performance as blood purification film improves. The approach of putting in PVP in the film has the common approach of causing phase separation and making carry out film formation by sending out the liquid within freezing characteristic from inner liquid at the same time it dissolves a polymer and PVP in a common solvent, and adds a non-solvent depending on the case, it considers as a spinning undiluted solution and it carries out the regurgitation from a nozzle, and shutting up PVP in the film.

[0003] However, although PVP which exists in a Polymer-rich phase in phase separation is in a polymer and a compatible condition within a polymer, PVP in a Polymer-lean phase turns into free PVP after coagulation. Free PVP has the danger of it being eluted into blood and causing an anaphylactic reaction at the time of blood contact. And although the polysulfone system polymer has the property of adsorbing endotoxin properly speaking, it is adding and carrying out hydrophilization of PVP, and an adsorption property is lost, mixing of endotoxin is seen and the case where a dialysis patient becomes feverish can see. There is also a report that an anaphylactic reaction arises because the elution of PVP and mixing of endotoxin take place to coincidence depending on the case, and the elution of PVP and mixing of endotoxin are the technical problems which should be avoided absolutely.

[0004] Moreover, since PVP eluted on the membranous outside intervenes, yarn adheres (fixing) and adhesion resin does not permeate the gap of yarn, when drying the film, when a bundle is used as a module, leak arises. Moreover, even if this module manufacture is possible, since a fixing part does not serve as a membranous effective area, it is inferior to the solute removal engine performance. In order to prevent fixing, the approach of twisting spacer yarn around yarn is also adopted, but while it is the process which requires time and effort very much, cost starts.

[0005] Thus, although a PVP's in film existence condition is a very important problem and PVP is the required matter in the field of an engine-performance manifestation, that the endotoxin adsorption capacity force is lost while becoming the cause of an anaphylactic reaction or fixing, if there is much free PVP poses a problem common to a polysulfone system hollow fiber.

[0006]

[Problem(s) to be Solved by the Invention] The hollow fiber excellent in module-assembly nature is obtained at the same time it reduces the danger of generation of heat under an anaphylactic reaction and dialysis.

[0007]

[Means for Solving the Problem] This inventions are as follows.

** The hollow fiber which is film which consists of a polysulfone system polymer and a polyvinyl pyrrolidone substantially, and is characterized by expressing the relation of the polyvinyl-pyrrolidone content (Ci) of a film internal surface, the polyvinyl-pyrrolidone content (Co) of a film outside surface, and the average polyvinyl-pyrrolidone content (Cave) in the film with a bottom type.

The hollow fiber given [above-mentioned] in ** the given endotoxin adsorption capacity force of $Ci \geq Cox3$ and the $Ci \geq Cavex2$ ** film is two or more 2000 EU/m.

** The hole density of a film outside surface is 25%. Hollow fiber the above-mentioned ** which it is above, or given in **.

** A hollow fiber given in either the above-mentioned ** manufactured by the spinning approach that more than air gap residence-time 0.5 second, the coagulation bath temperature of 70 degrees C or more, and nozzle temperature are lower than coagulation bath temperature 20 degrees C or more thru/or **.

** A hollow fiber given in either the above-mentioned ** obtained by washing this hollow fiber 30 seconds or more in hot water 80 degrees C or more after water 40 degrees C or more washes 1 minute or more in a spinning process thru/or **.

[0008]

[Embodiment of the Invention] The blood purification film in this invention consists of a polysulfone system polymer and a polyvinyl pyrrolidone (PVP) substantially. A polysulfone system polymer is a film material which is excellent in biocompatibility and a membranous fractionation property. Also in a polysulfone system polymer, polyether sulphone (PES) is desirable as a material of the field of biocompatibility and thermal resistance to the hemodialysis film. When using a polysulfone system polymer for the hemodialysis film, in order to control adhesion on the film of a plasma protein, PVP is used as a membranous hydrophilization agent in many cases. The ability as hemodialysis film can be demonstrated because include PVP in the film and it carries out hydrophilization..

[0009] However, when PVP is eluted from the film and goes into a dialysis patient's blood, there is a danger of triggering an anaphylactic shock reaction. Moreover, it is placed between the gaps of yarn by PVP eluted on the membranous outside, and yarn adheres (fixing of yarn). In the case of a module assembly, adhesion resin does not infiltrate into the gap of yarn, but, as for the bundle which fixed, leak takes place. That is, although PVP is very important in respect of an engine-performance manifestation, PVP beyond the need has a problem in respect of safety or module-assembly nature. Although especially PVP held in the blood contact surface at the film is indispensable in order to discover solute permeability ability, there is no semantics in which PVP exists in other film supporters parts.

[0010] Moreover, it is known that there is endotoxin adsorption capacity in a polysulfone system polymer. If PVP exists in a membranous supporters part mostly, endotoxin adsorption capacity will be spoiled by the hydrophilization effectiveness of PVP. There is also a report that the synergistic effect with PVP to which the patient was eluted in generation of heat when the endotoxin which exists in dialysing fluid entered into blood through the film triggers an anaphylactic shock reaction. Although each dialysis facility is tackling defecation of dialysing fluid, it is impossible to obtain dialysing fluid without endotoxin as a matter of fact. Then, if the endotoxin adsorption capacity force is in the film, endotoxin can prevent entering into a patient's blood. Therefore, it is better not to exist in other parts, although PVP is required for the blood contact surface absolutely.

[0011] Although how to fix to a hollow filament inside can be considered after carrying out spinning of the hollow filament if it is going to make PVP exist only in the blood contact surface, it is very difficult the field of cost, and in respect of being technical. Therefore, a polymer and PVP are supplied in the spinning undiluted solution, and the approach which the inside of the hollow filament which is the blood contact surface is made to localize in a spinning process is effective.

[0012] The hollow fiber in this invention extrudes the spinning undiluted solution which consists of a polymer, a non-solvent, PVP, and a solvent from the outside of a duplex spinneret, and after it is immersed to a coagulation bath through discharge and the air gap section, it can rinse and obtain a freezing characteristic liquid from the inside. Phase separation begins the extruded spinning undiluted solution with the liquid within freezing characteristic. PVP which exists in the Polymer-rich phase in phase separation is in a polymer and a compatible condition within a polymer, and after coagulation is

not eluted into blood, even if it is shut up in a polymer and the film contacts blood. However, PVP in a Polymer-lean phase is free, and it is necessary to flush it in the wash bath in a spinning process. As a result of flushing free PVP, PVP localizes to the compact layer of the blood contact surface, and the film with the low content of PVP is obtained by the membranous supporters part.

[0013] The relation between PVP content [on the content of PVP to 1 H-NMR and the polysulfone system polymer called for from a surface infrared absorption spectrum and as opposed to the polymer of a film internal surface] (C_i), and the PVP content (C_o) of a film outside surface and the average PVP content (C_{ave}) in the film is $C_i > C_o \times 3$ and $C_i > C_{ave} \times 2$. (formula 1)

At the time of **, PVP is concentrating on the film internal surface which is the blood contact surface, the PVP content of a supporters part becomes low, and it is desirable.

[0014] Although it is the approach of fully flushing free PVP, it is inadequate just to merely strengthen washing. The most important thing is making an outside surface puncture greatly in membranous structure. Washing effectiveness improves by making an outside surface puncture, and free PVP can fully be removed. When puncturing is not seen by the outside surface, PVP is prevented from free going away out of the film in the film. In that case, fixing of yarn occurs at the same time the PVP elution volume to the inside of blood increases.

[0015] 25% or more of the hole density of an outside surface is desirable. Washing effectiveness falls, and fixing of yarn generates 25% or less of case at the same time a PVP elution volume increases. The measuring method of outside-surface hole density photos the outside surface of a hollow filament sample by one 10,000 times the scale factor of this with a scanning electron microscope (SEM), copies a SEM image on the approach using an image processing system, or tracing paper, cuts off a puncturing part, and has a method of measuring and finding the weight of paper. Quantum nature has the highly desirable approach of searching for by the image processing also in it. It is desirable to use the image processing system image analyzer V20 by Toyobo Co., Ltd. as an approach of searching for by the image processing. By the TOKS method automatic binarization method, an aperture is made into white, others are made black, and it considers as outside-surface hole density in quest of the ratio of the area of a white part, and the whole area.

[0016] A means to gather the hole density of an outside surface lengthens AG die length in a dryness- and-moisture type spinning method, or it is effective to reduce spinning speed. That is, it is long and the residence time of the AG section is made into 0.5 seconds or more. The liquid within freezing characteristic can be made to determine membranous structure by lengthening the AG section residence time. That is, in order to avoid that a compact layer forms in an outside surface by strong coagulation from an outside surface, AG residence time is lengthened. The film is introduced to a coagulation bath, after structure is determined by inner liquid. By this approach, there is no compact layer in an outside surface, and the punctured film is obtained.

[0017] Although the film with which the outside surface punctured the residence time of the AG section by lengthening is obtained, just it is inadequate in order to gather hole density. In order to gather the hole density of an outside surface, existence of the moisture in the AG section is indispensable. The spinning undiluted solution breathed out from the duplex spinneret absorbs the steam which exists in the AG section, phase separation starts it, and the film which the outside surface punctured greatly is obtained. Specifically, outside-surface hole density can be made 25% or more by keeping the temperature of the AG section at 40 degrees C or more, and keeping humidity to 90% or more.

[0018] The concrete means which makes temperature of the AG section 40 degrees C or more, and makes humidity 90% or more has the effective approach of making coagulation bath temperature of 70 degrees C or more, and nozzle temperature lower 20 degrees C or more than coagulation bath temperature. The phase separation of an outside surface is promoted with the steam which evaporates from a coagulation bath.

[0019] After making a membranous outside surface puncture to 25% or more, it is necessary to fully wash. In a spinning process, after 40-degree C water washes washing 1 minute or more, its approach of washing 30 seconds or more in 80-degree C hot water is effective. Thus, in order to carry out long duration washing at a spinning process, an easy approach uses the Nelson roller.

[0020] In this way, only a predetermined number can bundle the obtained hollow fiber, resin adhesion can be carried out, and a module can be obtained by starting an edge. Optimum dose mixing of tap

water and the reverse osmosis (RO) water was carried out, 5L adjustment of Et liquid of about 3000 EU/L was done, and it put into the beaker, and in order to measure the modular endotoxin amount of adsorption, from the modular dialysing fluid inlet port, Et liquid is introduced by the rate of flow of 500 ml/min, and it filters to the hollow filament inside by filtration flow rate 100 ml/min, and filtrate and dialysing fluid outlet liquid are returned to the original beaker, and were circulated for 2 hours. By measuring the endotoxin concentration in the beaker circulation before and after circulation, the quantum of the amount of endotoxins which stuck to the film can be carried out. The endotoxin amount of adsorption is so desirable that it is high in order to bar endotoxin mixing into blood. The quantum was carried out to measurement of endotoxin concentration by measuring nephelometry time amount in the TOKISHINO meter ET 201 using Wako Pure Chem RIMURUSU ES-II Test Wako.

[0021]

[Example] Although an example is given to below and this invention is explained, this invention is not limited at all.

[0022] Polyether sulphone (PES) a polyvinyl pyrrolidone (K-90) to a hydrophilization agent 17.0% of the weight 3.0 % of the weight, (Example 1) Inner liquid concentration (DMAC+ water) to a solvent water dimethylacetamide (DMAC) 75.0% 5.0% of the weight as a non-solvent as 50% After making into 0.6 seconds, discharge, AG die length of 600mm, and a part for /, i.e., the spinning speed AG residence time of 60m, the outside of the duplex spinneret which kept the spinning undiluted solution at 40 degrees C to inner liquid from the inside of a duplex spinneret, After being immersed to the coagulation bath of 10% of 70-degree C coagulation bath concentration (DMAC+ water), 45 degrees C of pure water wash for 45 seconds at 80 degrees C of pure water for 1 minute, and it rolls round to skein, and it is the bore of 198.2 micrometers. The hollow fiber of 29.4 micrometers of thickness was obtained. The temperature of the AG section in a 250mm part is 45 degrees C from the nozzle at this time, humidity is 95%, and it is thought that the phase separation of an outside surface can be promoted with the moisture of the AG section.

[0023] The outside-surface SEM image (one 10,000 times the scale factor of this) of the obtained hollow fiber is shown in drawing 1 . an outside-surface SEM photograph -- the image analyzer V20 by Toyobo Co., Ltd. -- using -- TOKS -- law -- the image which performed the image processing in binarization is shown in drawing 2 . The outside-surface hole density searched for from now on was 30.1%.

[0024] Fixing of yarn was not observed at all, but while the module assembly was easy, the channeling of dialysing fluid was not seen, but the solute removal engine performance needed as shown in Table 1 was able to be discovered. The module of 2 was assembled 1.5m of film surface products, and when the amount of PVP eluted from a module using an ethanol water solution 40% was measured, it was thought that they were completely satisfactory even if 1.5mg and the amount of those are slight and it uses them by clinical.

[0025] PVP part clothes volume at this time The quantum was carried out in the following ways using 1 H-NMR spectrum and the infrared absorption spectrum.

(1) It is 1 H-NMR spectrum hollow fiber DMSO-d6 It was made to dissolve and 1 H-NMR spectrum was measured at 60 degrees C. measurement -- the product made from Varian -- Unity-500 (at the time of H measurement 500MHz) was used. 1 From the integrated-intensity ratio of the peak (four protons /repeat unit) of the ring origin of the polysulfone system polymer near [in a H-NMR spectrum] 7.2 ppm, and the peak (four protons /repeat unit) of the pyrrolidone ring origin of 1.8-2.2 ppm PVP, the average PVP content Cave in the film (wt%) was computed.

[0026] (2) Infrared absorption spectrum (FT-IR spectrum)

Measurement of the outside surface in the film performed measurement of an ATR method and the whole film with the transmission method. In measurement, it is SPECTRA. Product made from TECH IRmus/SIRM was used. In the ATR method, diamond 45 degree was used as an internal reflection element. the ratio of the absorption intensity A_p of the peak originating in C=O of PVP of 1675cm⁻¹ in an infrared absorption spectrum, and the absorption intensity A_s of the peak in which the polysulfone system polymer of the 1580cm⁻¹ neighborhood originates -- A_p/A_s was calculated. since absorption intensity is dependent on the measurement wave number in an ATR method -- as correction value -- the peak location ν_u of a polysulfone system polymer -- the ratio of peak location ν_{up} (wave number) of s and PVP -- ν_p/ν_s was applied to the actual measurement.

[0027] Internal-surface PVP content (Ci) and the PVP content (Co) of an outside surface were computed from the following formulas.

$Ci = CavexRi / Rt$ (formula 2)

$Co = CavexRo / Rt$ (formula 3)

Cave: PVP content Ri for which it asked from 1 H-NMR: FT-IR PVP of an internal surface and the extinction quotient of a polysulfone system polymer (after amendment) in an ATR method

Ro : FT-IR PVP of an outside surface and the extinction quotient of a polysulfone system polymer (after amendment) in an ATR method

Rt : Extinction quotient of PVP in a FT-IR transmission method, and a polysulfone system polymer

[0028] Film obtained on the above-mentioned spinning conditions 1 H-NMR spectrum is shown in drawing 3, and an enlarged drawing is shown in drawing 4. The chart according the chart by the infrared extinction spectrum ATR method to an infrared extinction spectrum transmission method is shown in drawing 5 at drawing 6. 3.0%, the PVP content of an internal surface and an outside surface is 8.3% and 1.7%, respectively, and the average PVP content Cave for which it asked from these charts was filling the formula 1. The module was obtained by it being filled up with these 9976 hollow filaments to a case, pasting up by resin, and starting an edge with a cutting edge. The modular filling factor was [24.0cm and effective length's film surface product] 2 1.49m 57%. The endotoxin adsorption test was performed using this module.

[0029] That is, it was made to circulate by mixing tap water and Milli Q water using Et liquid of 3160 EU/L by dialysing fluid inlet-port flow rate 500 ml/min and filtration flow rate 100 ml/min. The endotoxin concentration of Et liquid of 2 hours after was 2140 EU/L, and the endotoxin amount of adsorption was 5100EU, and when it was changed to per unit membrane area, it was 3400 EU/m². In addition, Et concentration of the filtrate under measurement is below limit of detection, and endotoxin mixing was suppressed.

[0030] Polyether sulphone (PES) Polyvinylpyrrolidone K90 (K90) to a hydrophilization agent 17.0% of the weight 3.0 % of the weight, (Example 1 of a comparison) Inner liquid concentration (DMAC+ water) to a solvent water dimethylacetamide (DMAC) 75.0% 5.0% of the weight as a non-solvent as 60% After making into 0.1 seconds, discharge, AG die length of 50mm, and a part for /, i.e., the spinning speed AG residence time of 30m, the outside of the duplex spinneret which kept the spinning undiluted solution at 40 degrees C to inner liquid from the inside of a duplex spinneret, After being immersed to the coagulation bath of 30% of 40-degree C coagulation bath concentration (DMAC+ water), 45 degrees C of pure water washed for 45 seconds at 80 degrees C of pure water for 1 minute, it rolled round to skein, and the hollow fiber of 30 micrometers of thickness was obtained. The temperature of the AG section in a 25mm part was 38 degrees C from the nozzle at this time, and humidity was 80%. The outside-surface SEM image (one 10,000 times the scale factor of this) of the obtained hollow fiber is shown in drawing 7. An aperture was not seen at all by the outside surface, but it was considered that outside-surface hole density was 0%. When yarn was dried, fixing of yarn was violently impossible for the modularization.

[0031] They are an example 1 and this appearance about the PVP part clothes volume at this time. When the quantum was carried out using 1 H-NMR and FT-IR, the average PVP content in the film was 4.0%. The PVP content of an internal surface and an outside surface was 5.0% and 6.0%, respectively, and there were very many PVP contents of an outside surface.

[0032]

[Table 1]

	実施例 1	比較例 1
膜厚 (μm)	30	30
ノズル温度 (°C)	40	40
AG 滞留時間 (sec)	0.6	0.1
AG 部温度 (°C)	45	38
AG 部湿度 (%)	95	80
凝固浴温度 (°C)	70	40
外表面開孔率 (%)	30.1	0.0
PVP 溶出量 (mg)	1.5	モジュール組立不可
エンドトキシン吸着量 (EU/m ²)	3400	モジュール組立不可
膜内の平均 PVP 含有率 (Cave)	3.0	4.0
膜内表面の PVP 含有率 (Ci)	8.3	5.0
膜外表面の PVP 含有率 (Co)	1.7	6.0

[Translation done.]

* NOTICES *

JPO and NCIP are not responsible for any damages caused by the use of this translation.

1.This document has been translated by computer. So the translation may not reflect the original precisely.

2.*** shows the word which can not be translated.

3.In the drawings, any words are not translated.

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1] The scanning electron microscope photograph (one 10,000 times the scale factor of this) of the outside surface of the hollow fiber obtained in the example 1 is shown.

[Drawing 2] the outside-surface scanning electron microscope photograph of drawing 1 -- the image analyzer V20 by Toyobo Co., Ltd. -- using -- TOKS -- law -- the image which performed the image processing in binarization is shown.

[Drawing 3] Hollow fiber obtained in the example 1 1 H-NMR spectrum is shown.

[Drawing 4] Hollow fiber obtained in the example 1 The enlarged drawing of 1 H-NMR spectrum is shown.

[Drawing 5] The chart by the infrared extinction spectrum ATR method of the hollow fiber obtained in the example 1 is shown.

[Drawing 6] The chart by the infrared extinction spectrum transmission method of the hollow fiber obtained in the example 1 is shown.

[Drawing 7] The scanning electron microscope photograph (one 10,000 times the scale factor of this) of the outside surface of the hollow fiber obtained in the example 1 of a comparison is shown.

[Translation done.]

* NOTICES *

JPO and NCIPi are not responsible for any damages caused by the use of this translation.

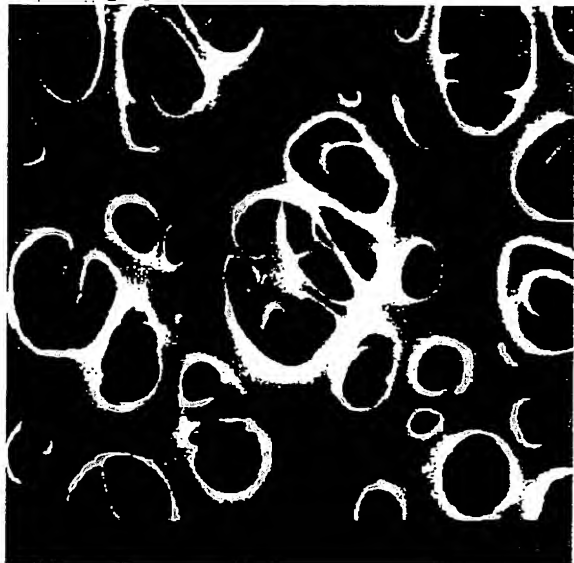
1.This document has been translated by computer. So the translation may not reflect the original precisely.

2.*** shows the word which can not be translated.

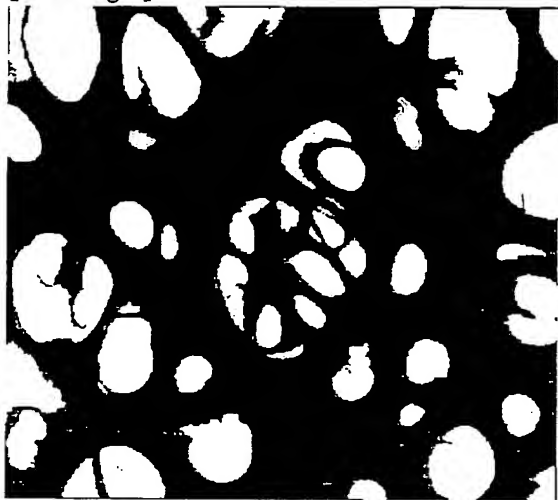
3.In the drawings, any words are not translated.

DRAWINGS

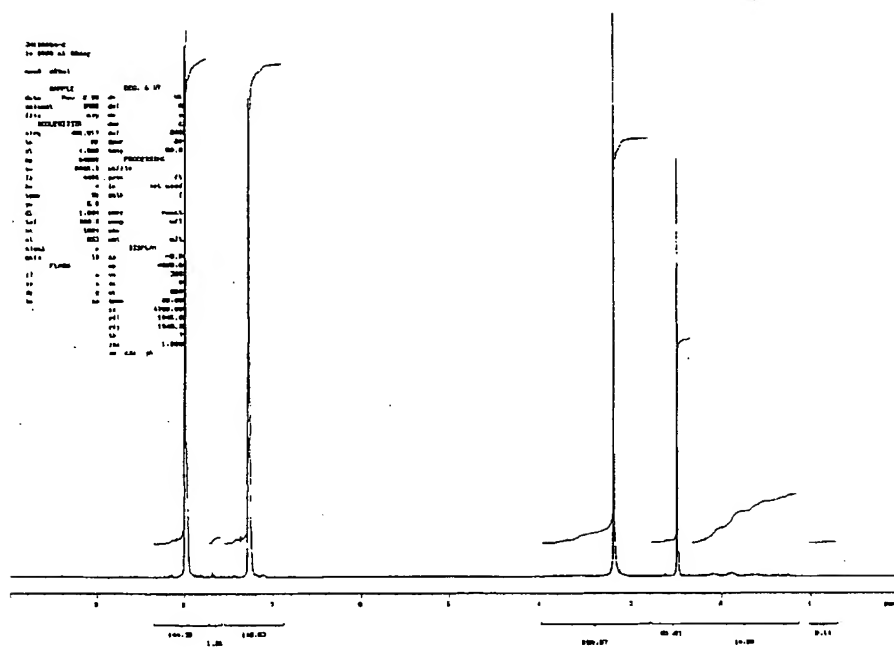
[Drawing 1]



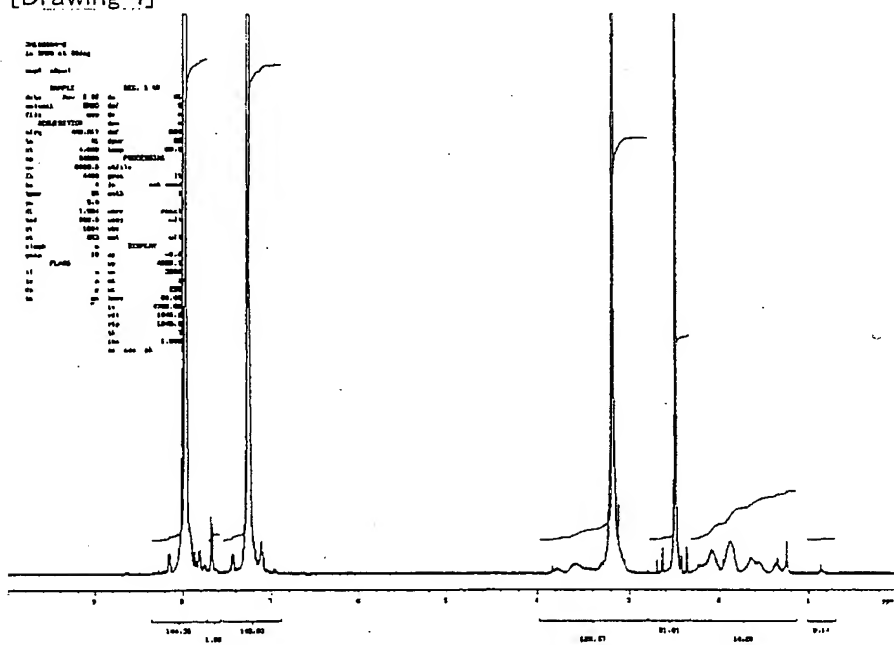
[Drawing 2]



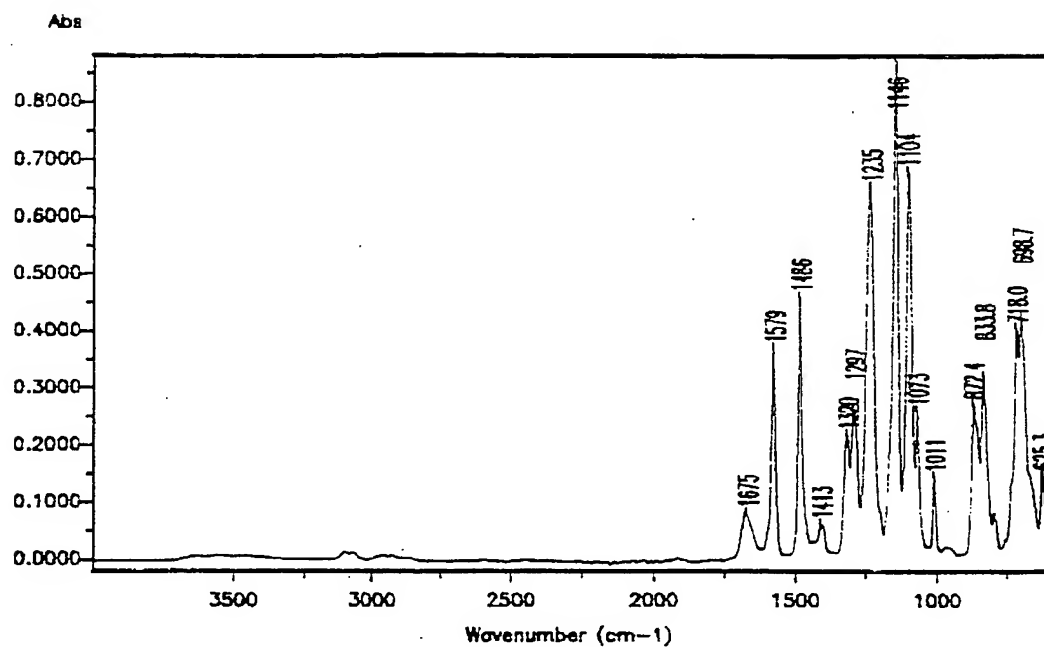
[Drawing 3]



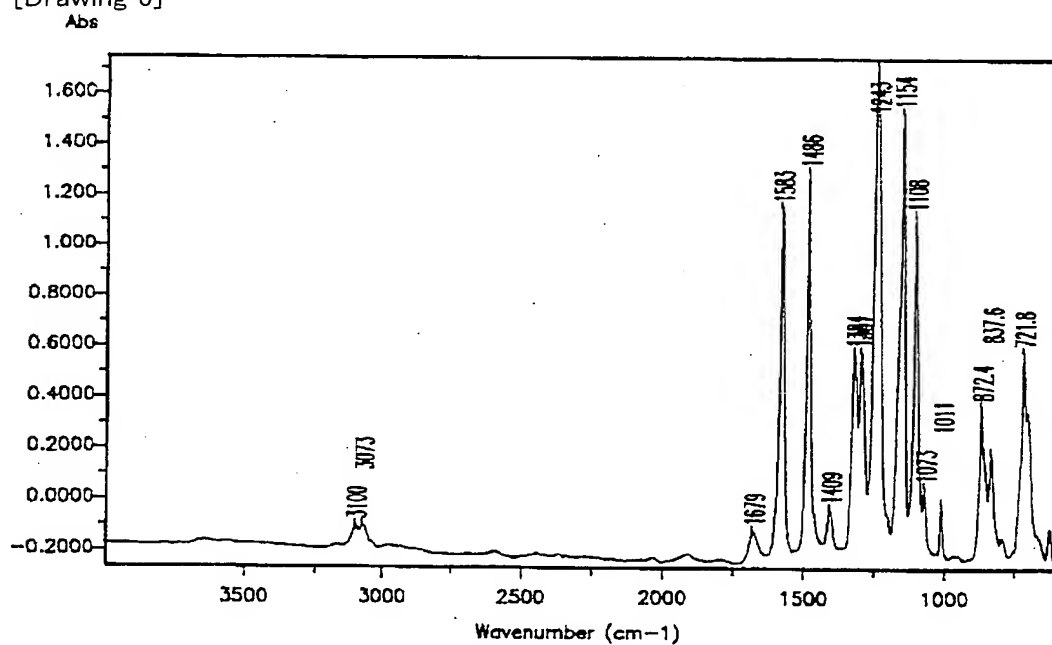
[Drawing 4]



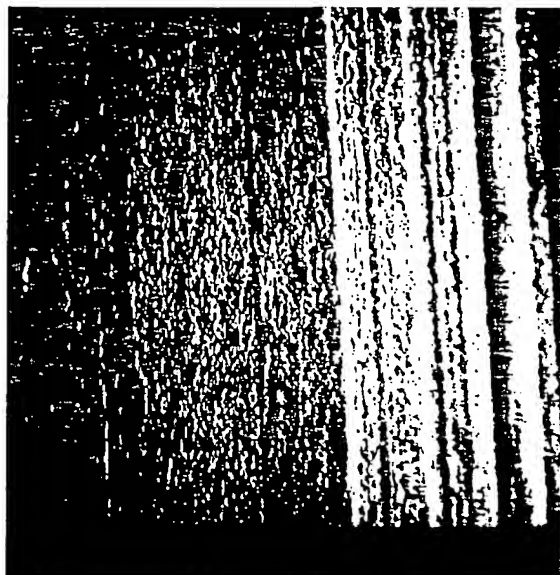
[Drawing 5]



[Drawing 6]



[Drawing 7]



[Translation done.]

Best Available Copy

(19) 日本国特許庁 (J P)

(12) 公開特許公報 (A)

(11) 特許出願公開番号
特開2001-38170
(P2001-38170A)

(43) 公開日 平成13年2月13日 (2001.2.13)

(51) Int.Cl. ⁷	識別記号	F I	キーワード (参考)
B 0 1 D 69/08		B 0 1 D 69/08	4 D 0 0 6
71/44		71/44	
71/68		71/68	

審査請求 未請求 請求項の数 4 O L (全 9 頁)

(21) 出願番号 特願平11-219912

(22) 出願日 平成11年8月3日 (1999.8.3)

(71) 出願人 000003160

東洋紡績株式会社

大阪府大阪市北区堂島浜2丁目2番8号

(72) 発明者 京 基樹

滋賀県大津市堅田二丁目1番1号 東洋紡績株式会社総合研究所内

(72) 発明者 加藤 典昭

滋賀県大津市堅田二丁目1番1号 東洋紡績株式会社総合研究所内

(72) 発明者 土屋 俊之

滋賀県大津市堅田二丁目1番1号 東洋紡績株式会社総合研究所内

最終頁に続く

(54) 【発明の名称】 中空糸膜

(57) 【要約】

【課題】 アナフィラキシー反応、透析中の発熱の危険性を低減すると同時に、モジュール組立性に優れた中空糸膜を提供する。

【解決手段】 実質的にポリスルホン系ポリマーとポリビニルピロリドンからなる膜であり、膜内表面のポリビニルピロリドン含有率 (C_i) と膜外表面のポリビニルピロリドン含有率 (C_o)、膜内の平均ポリビニルピロリドン含有率 (C_{ave}) の関係が下式で表されることを特徴とする中空糸膜。

$$C_i \geq C_o \times 3, C_i \geq C_{ave} \times 2$$

SS
CC
aa
nn
nn
ee
dd

11
22
77
88
22
50
50
55

(2)

特開 2001-38170

2

【特許請求の範囲】

【請求項 1】 実質的にポリスルホン系ポリマーとポリビニルピロリドンからなる膜であり、膜内表面のポリビニルピロリドン含有率（Ci）と膜外表面のポリビニルピロリドン含有率（Co）、膜内の平均ポリビニルピロリドン含有率（Cave）の関係が下式で表されることを特徴とする中空糸膜。

$$Ci \geq Co \times 3, Ci \geq Cave \times 2$$

【請求項 2】 膜のエンドトキシン吸着能力が 2000 EU/m^2 以上である請求項 1 記載の中空糸膜。

【請求項 3】 膜外表面の開孔率が 25% 以上である請求項 1 または 2 記載の中空糸膜。

【請求項 4】 紡糸工程において 40°C 以上の水で 1 分以上洗浄した後、 80°C 以上の熱水中で 30 秒以上、該中空糸膜を洗浄することによって得られうる請求項 1 ないし 4 のいずれかに記載の中空糸膜。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】 本発明は新規な中空糸膜に関する。詳しくは腎不全などの治療に用いる膜であり、アナフィラキシー反応の発生が少なく、エンドトキシンの混入を吸着によって阻止することができるため安全性が高く、かつモジュール組立性に優れた血液浄化膜に関する。

【0002】

【従来の技術】 ポリスルホン系ポリマーを原料とする血液浄化膜には、膜の親水化剤としてポリビニルピロリドン（PVP）を使用するのがほとんどである。PVP を使用すると膜が親水化されるために、膜面への血漿蛋白の吸着を抑制することができ、膜の分画特性が向上し、血液浄化膜としての性能が向上する。PVP を膜内に入れる方法は、ポリマーと PVP を共通溶媒に溶解させ、場合によっては非溶媒を加えて紡糸原液とし、ノズルから吐出すると同時に内液から凝固性内液を送り出すことで相分離を引き起こし膜形成させて、膜内に PVP を閉じこめる方法が一般的である。

【0003】 しかし、相分離において Polymer-rich 相に存在する PVP はポリマー内にてポリマーと相溶状態にあるが、Polymer-lean 相における PVP は凝固後にフリーの PVP となる。フリーの PVP は血液接触時に血液中へと溶出しアナフィラキシー反応を起こす危険性がある。しかも本来ならば、ポリスルホン系ポリマーはエンドトキシンを吸着する特性を有しているが、PVP を加えて親水化することで、吸着特性を失い、エンドトキシンの混入がみられ、透析患者が発熱する場合が見受けられる。場合によっては PVP の溶出とエンドトキシンの混入が同時に起こることでアナフィラキシー反応が生じるとの報告もあり、PVP の溶出とエンドトキシンの混入は絶対に避けるべき課題である。

【0004】 また、膜を乾燥させたときに膜の外側に溶出した PVP が介在して糸同士がくっつき（固着）、糸の間に接着樹脂が浸透しないためにバンドルをモジュールとしたときにリークが生じる。また本モジュール製作が可能だったとしても固着部分は膜の有効面積とならないために溶質除去性能に劣る。固着を防ぐために糸にスペーサーヤーンを巻き付ける方法も採用されているが、非常に手間がかかる工程であると同時にコストがかかる。

10 【0005】 このように膜内の PVP の存在状態は非常に重要な問題であり、PVP は性能発現の面で必要な物質であるが、フリーの PVP が多いとアナフィラキシー反応や固着の原因となるとともにエンドトキシン吸着能力が失われることが、ポリスルホン系中空糸膜に共通の問題となっている。

【0006】

【発明が解決しようとする課題】 アナフィラキシー反応、透析中の発熱の危険性を低減すると同時に、モジュール組立性に優れた中空糸膜を得る。

20 【0007】

【課題を解決するための手段】 本発明は以下のものである。

① 実質的にポリスルホン系ポリマーとポリビニルピロリドンからなる膜であり、膜内表面のポリビニルピロリドン含有率（Ci）と膜外表面のポリビニルピロリドン含有率（Co）、膜内の平均ポリビニルピロリドン含有率（Cave）の関係が下式で表されることを特徴とする中空糸膜。

$$Ci \geq Co \times 3, Ci \geq Cave \times 2$$

30 ② 膜のエンドトキシン吸着能力が 2000 EU/m^2 以上である上記①記載の中空糸膜。

③ 膜外表面の開孔率が 25% 以上である上記①または②記載の中空糸膜。

④ エアギャップ滞留時間 0.5 秒以上、凝固浴温度 70°C 以上、ノズル温度が凝固浴温度より 20°C 以上低い紡糸方法にて製造する上記①ないし③のいずれかに記載の中空糸膜。

40 ⑤ 紡糸工程において 40°C 以上の水で 1 分以上洗浄した後、 80°C 以上の熱水中で 30 秒以上、該中空糸膜を洗浄することによって得られる上記①ないし④のいずれかに記載の中空糸膜。

【0008】

【発明の実施の形態】 本発明における血液浄化膜は実質的にポリスルホン系ポリマーとポリビニルピロリドン（PVP）からなる。ポリスルホン系ポリマーは生体適合性と膜の分画特性に優れた膜素材である。ポリスルホン系ポリマーの中でも、ポリエーテルスルホン（PES）が生体適合性と耐熱性の面から血液透析膜の素材として好ましい。ポリスルホン系ポリマーを血液透析膜に使用する場合、血漿蛋白の膜への付着を抑制するため膜

の親水化剤としてPVPを使用することが多い。PVPを膜内に含ませて親水化することで血液透析膜としての実力を発揮することができる。

【0009】しかし、PVPが膜から溶出し透析患者の血液に入るとアナフィラキシーショック反応を引き起こす危険性がある。また、膜の外側に溶出したPVPは糸の間隙に介在して、糸同士がくっつく（糸の固着）。固着したバンドルはモジュール組立の際に糸の間隙に接着樹脂が浸入せずリークが起こる。すなわちPVPは性能発現の点で非常に重要であるにもかかわらず、必要以上のPVPは安全性やモジュール組立性の面で問題がある。特に、血液接触面において、膜に保持されたPVPは溶質透過性能を発現するためには不可欠であるものの、その他の膜支持層部分でPVPが存在する意味はない。

【0010】また、ポリスルホン系ポリマーにはエンドトキシン吸着能があることが知られている。膜の支持層部分にPVPが多く存在すると、PVPの親水化効果により、エンドトキシン吸着能が損なわれる。透析液中に存在するエンドトキシンが膜を介して血液の中に入ると患者が発熱、中には溶出したPVPとの相乗効果によりアナフィラキシーショック反応を引き起こすとの報告もある。各透析施設は透析液の清浄化に取り組んでいるものの、エンドトキシンが全くない透析液を得ることは事実上不可能である。そこで、膜にエンドトキシン吸着能力があれば、エンドトキシンが患者の血液中へ入るのを阻止できる。よって、PVPは血液接触面には絶対必要であるが、その他の部分には存在しない方がよい。

【0011】血液接触面だけにPVPを存在させようとすると、中空糸を紡糸してから中空糸内面に固定する方法が考えられるが、コストの面、技術的な面で非常に困難である。よって、ポリマーとPVPを紡糸原液の中に投入しておき、紡糸工程において血液接触面である中空糸の内面に局在化させる方法が効果的である。

【0012】本発明における中空糸膜は、ポリマーと非溶媒とPVPと溶媒からなる紡糸原液を二重紡糸口金の外側から押し出し、内側から凝固性液体を吐出し、エアギャップ部を経て凝固浴へと浸漬した後、水洗して得ることができる。押し出された紡糸原液は凝固性内液によって相分離が始める。相分離におけるPolymer-rich相に存在するPVPはポリマー内にてポリマーと相溶状態にあり、凝固後はポリマー内に閉じこめられて、膜が血液と接触しても、血液中へと溶出ししない。しかし、Polymer-lean相におけるPVPはフリーであり、紡糸工程における水洗浴にて洗い流す必要がある。フリーのPVPを洗い流した結果、血液接触面の緻密層にPVPが局在化し、膜の支持層部分にはPVPの含有率が低い膜が得られる。

【0013】¹H-NMRおよび、表面赤外吸収スペクトルより求められるポリスルホン系ポリマーに対するP

VPの含有率において、膜内表面のポリマーに対するPVP含有率(C_i)と膜外表面のPVP含有率(C_o)、膜内の平均PVP含有率(C_{ave})の関係が $C_i \geq C_o \times 3$ 、 $C_i \geq C_{ave} \times 2$ (式1)のとき、血液接触面である膜内表面にPVPが集中しており、支持層部分のPVP含有量が低くなり、好ましい。

【0014】フリーのPVPを十分に洗い流す方法であるが、ただ単に洗浄を強化するだけでは不十分である。最も重要なことは、膜の構造において外表面を大きく開孔させることである。外表面を開孔させることで洗浄効率が向上し、フリーのPVPを十分に除去できる。外表面に開孔がみられない場合は、膜内のフリーのPVPが膜外へと出ていくのが妨げられる。その場合、血液中へのPVP溶出量が増大すると同時に、糸の固着が発生する。

【0015】外表面の開孔率は25%以上が好ましい。25%以下の場合は洗浄効率が落ち、PVP溶出量が増大すると同時に糸の固着が発生する。外表面開孔率の測定方法は、中空糸サンプルの外表面を走査型電子顕微鏡(SEM)で倍率10,000倍にて撮影し、画像処理装置を用いる方法、あるいはトレーシングペーパーでSEM像を写しとって、開孔部分を切り取り、紙の重量を測定して求める方法がある。その中でも画像処理で求める方法が定量性が高く好ましい。画像処理で求める方法としては東洋紡績株式会社製画像処理装置イメージアナライザーV20を用いるのが好ましい。TOKS法自動二値化法により開孔部を白色、その他を黒色とし、白色部分の面積と全体の面積の比を求めて外表面開孔率とする。

【0016】外表面の開孔率をあげる手段は乾湿式紡糸法におけるAG長さを長くする、あるいは紡速を低下させるのが有効である。すなわち、AG部の滞留時間を長く、0.5秒以上とする。AG部滞留時間を長くすることで凝固性内液によって膜の構造を決定させることができる。すなわち、外表面からの強い凝固によって外表面に緻密層が形成するのを避けるためにAG滞留時間を長くする。膜は内液によって構造が決定された後に凝固浴へと導入される。この方法によって外表面に緻密層がなく、開孔した膜が得られる。

【0017】AG部の滞留時間を長くすることで、外表面が開孔した膜が得られるが、開孔率を上げるためには、それだけでは不十分である。外表面の開孔率を上げるためには、AG部における水分の存在が不可欠である。二重紡糸口金から吐出した紡糸原液はAG部に存在する水蒸気を吸収して相分離が起こり、外表面が大きく開孔した膜が得られる。具体的には、AG部の温度を40℃以上、湿度を90%以上に保つことで、外表面開孔率を25%以上にすることができる。

【0018】AG部の温度を40℃以上、湿度を90%

以上にする具体的手段は凝固浴温度70℃以上、ノズル温度を凝固浴温度より20℃以上低くする方法が有効である。凝固浴から蒸発する水蒸気によって、外表面の相分離を促進する。

【0019】膜の外表面を25%以上に開孔させたうえで、十分に洗浄を実施する必要がある。洗浄は紡糸工程において、1分以上40℃の水で洗浄した後、80℃の熱水中で30秒以上洗浄する方法が効果的である。このように紡糸工程にて長時間洗浄するためにはネルソンローラーを用いるのが容易な方法である。

【0020】こうして得られた中空糸膜を所定の本数だけ束ねて樹脂接着し、端部を切り出すことでモジュールを得ることができる。モジュールのエンドトキシン吸着量を測定するには、水道水と逆浸透(RO)水を適量混合して約3000EU/LのEt液を5L調整してビーカーに入れ、モジュールの透析液入口よりEt液を500ml/minの流速で導入し、濾過流量100ml/minで中空糸内側へと濾過し、濾過液と透析液出口液を元のビーカーに戻し、二時間循環させた。循環前と循環後のビーカー内のエンドトキシン濃度を測定することで、膜に吸着したエンドトキシン量を定量することができる。エンドトキシン吸着量は高いほど、血液中へのエンドトキシン混入を妨げるため好ましい。エンドトキシン濃度の測定には和光純薬製のリムルスES-11テストワコーを用い、トキシノメーターET201にて比濁時間の測定をすることで定量した。

【0021】

【実施例】以下に実施例を挙げて、本発明を説明するが、本発明はなんら限定されるものではない。

【0022】(実施例1) ポリエーテルスルホン(PES)が17.0重量%、親水化剤にポリビニルピロリドン(K-90)を3.0重量%、非溶媒として水を5.0重量%、溶媒にジメチルアセトアミド(DMAC)75.0%、内液濃度(DMAC+水)が50%として、紡糸原液を40℃に保った二重紡糸口金の外側から、内液を二重紡糸口金の内側から吐出し、AG長さ600mm、紡速60m/分、すなわちAG滞留時間0.6秒としたあと、70℃の凝固浴濃度(DMAC+水)10%の凝固浴へと浸漬した後、純水45℃にて1分間、純水80℃にて45秒間洗浄し、カセへと巻き取り、内径198.2μm、膜厚29.4μmの中空糸膜を得た。このときのノズルから250mmの部分におけるAG部の温度は45℃、湿度は95%であり、AG部の水分によって外表面の相分離を促進できていると考えられる。

【0023】得られた中空糸膜の外表面SEM像(倍率10,000倍)を図1に示す。外表面SEM写真を、東洋紡績株式会社製イメージアナライザーV20を用いTOKS法二値化にて画像処理を行った画像を図2に示す。これから求めた外表面開孔率は30.1%であった。

【0024】糸の固着は全く観察されず、モジュール組立は容易であると同時に、透析液のチャネリングはみられず、表1に示すように必要とされる溶質除去性能は発現できていた。膜面積1.5m²のモジュールを組み立て、40%エタノール水溶液を使ってモジュールから溶出するPVPの量を測定したところ、1.5mgとその量は軽微であり、臨床で使用しても全く問題がないと考えられた。

【0025】このときのPVP分布量を¹H-NMRスペクトルと赤外吸収スペクトルを用い、以下の要領で定量した。

(1) ¹H-NMRスペクトル

中空糸膜をDMSO-d₆に溶解させ、60℃で¹H-NMRスペクトルを測定した。測定にはVarian社製Unity-500(H測定時500MHz)を使用した。¹H-NMRスペクトルにおける7.2ppm付近のポリスルホン系ポリマーの芳香環由来のピーク(プロトン4個分/繰り返し単位)と1.8~2.2ppmのPVPのピロリドン環由来のピーク(プロトン4個分/繰り返し単位)の積分強度比より、膜内の平均PVP含有率Cave(wt%)を算出した。

【0026】(2) 赤外吸収スペクトル(FT-IRスペクトル)

膜内外表面の測定はATR法、膜全体の測定は透過法にて行った。測定にはSPECTRA TECH社製IRμs/SIRMを使用した。ATR法では内部反射エレメントとしてダイヤモンド45°を使用した。赤外吸収スペクトルにおける1675cm⁻¹のPVPのC=Oに由来するピークの吸収強度Apと1580cm⁻¹付近のポリスルホン系ポリマーが由来するピークの吸収強度Asの比Ap/Asを求めた。ATR法においては吸収強度が測定波数に依存しているため、補正值としてポリスルホン系ポリマーのピーク位置νsおよびPVPのピーク位置νp(波数)の比νp/νsを実測値にかけた。

【0027】内表面PVP含有率(Ci)および外表面のPVP含有率(Co)は以下の式より算出した。

$$C_i = C_{ave} \times R_i / R_t \quad (式2)$$

$$C_o = C_{ave} \times R_o / R_t \quad (式3)$$

Cave: ¹H-NMRより求めたPVP含有率

Ri: FT-IR ATR法における内表面のPVPとポリスルホン系ポリマーの吸光度比(補正後)

Ro: FT-IR ATR法における外表面のPVPとポリスルホン系ポリマーの吸光度比(補正後)

Rt: FT-IR透過法におけるPVPとポリスルホン系ポリマーの吸光度比

【0028】上記紡糸条件にて得られた膜の¹H-NMRスペクトルを図3に、拡大図を図4に示す。赤外吸収スペクトルATR法によるチャートを図5に、赤外吸収スペクトル透過法によるチャートを図6に示す。これら

のチャートから求めた平均PVP含有率Caveは3.0%、内表面と外表面のPVP含有率はそれぞれ8.3%、1.7%であり、式1を満たしていた。この中空糸9976本をケースへ充填して樹脂で接着し、端部を刃で切り出すことでモジュールを得た。モジュールの充填率は57%、有効長は24.0cm、膜面積は1.49m²だった。このモジュールを用いてエンドトキシン吸着テストを行った。

【0029】すなわち、水道水と逆浸透水を混ぜ合わせることで、3160EU/LのEt液を用い、透析液入口流量500ml/min、濾過流量100ml/minで循環させた。二時間後のEt液のエンドトキシン濃度は2140EU/Lであり、エンドトキシン吸着量は5100EUであり、単位膜面積あたりに直すと、3400EU/m²であった。なお、測定中の濾過液のEt濃度は検出限界以下でありエンドトキシン混入が抑えられていた。

【0030】(比較例1) ポリエーテルスルホン(PES)が17.0重量%、親水化剤にポリビニルピロリドンK-90(K90)を3.0重量%、非溶媒として水20を5.0重量%、溶媒にジメチルアセトアミド(DMA*

*C) 75.0%、内液濃度(DMAC+水)が60%として、紡糸原液を40℃に保った二重紡糸口金の外側から、内液を二重紡糸口金の内側から吐出し、AG長さ50mm、紡速30m/分、すなわちAG滞留時間0.1秒としたあと、40℃の凝固浴濃度(DMAC+水)30%の凝固浴へと浸漬した後、純水45℃にて1分間、純水80℃にて45秒間洗浄し、カセへと巻き取り、膜厚30μmの中空糸膜を得た。このときのノズルから25mmの部分におけるAG部の温度は38℃、湿度は80%であった。得られた中空糸膜の外表面SEM像(倍率10,000倍)を図7に示す。外表面には全く開孔部がみられず、外表面開孔率は0%とみなされた。糸を乾燥させたところ、糸の固着が激しくモジュール化は不可能であった。

【0031】このときのPVP分布量を実施例1と同様に¹H-NMRとFT-IRを用いて定量したところ、膜内の平均PVP含有率は4.0%であった。内表面と外表面のPVP含有率はそれぞれ5.0%、6.0%であり、外表面のPVP含有量が非常に多かった。

【0032】

【表1】

	実施例1	比較例1
膜厚(μm)	30	30
ノズル温度(℃)	40	40
AG滞留時間(sec)	0.6	0.1
AG部温度(℃)	45	38
AG部湿度(%)	95	80
凝固浴温度(℃)	70	40
外表面開孔率(%)	30.1	0.0
PVP溶出量(mg)	1.5	モジュール組立不可
エンドトキシン吸着量(EU/m ²)	3400	モジュール組立不可
膜内の平均PVP含有率(Cave)	3.0	4.0
膜内表面のPVP含有率(Ci)	8.3	5.0
膜外表面のPVP含有率(Co)	1.7	6.0

【図面の簡単な説明】

【図1】実施例1で得られた中空糸膜の外表面の走査型電子顕微鏡写真(倍率10,000倍)を示す。

【図2】図1の外表面走査型電子顕微鏡写真を、東洋紡績株式会社製イメージアナライザーV20を用いTOKS法二値化にて画像処理を行った画像を示す。

【図3】実施例1で得られた中空糸膜の¹H-NMRスペクトルを示す。

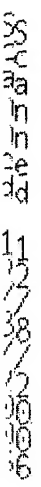
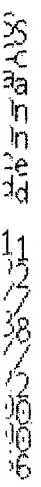
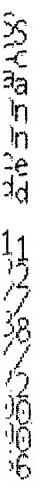
【図4】実施例1で得られた中空糸膜の¹H-NMRスペクトルの拡大図を示す。

【図5】実施例1で得られた中空糸膜の赤外吸光スペクトルATR法によるチャートを示す。

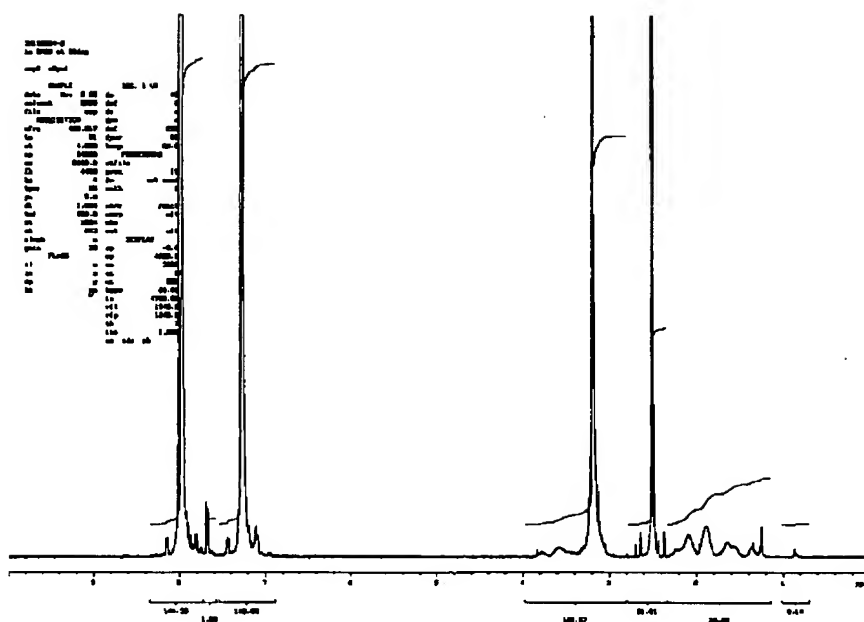
【図6】実施例1で得られた中空糸膜の赤外吸光スペクトル透過法によるチャートを示す。

【図7】比較例1で得られた中空糸膜の外表面の走査型電子顕微鏡写真(倍率10,000倍)を示す。

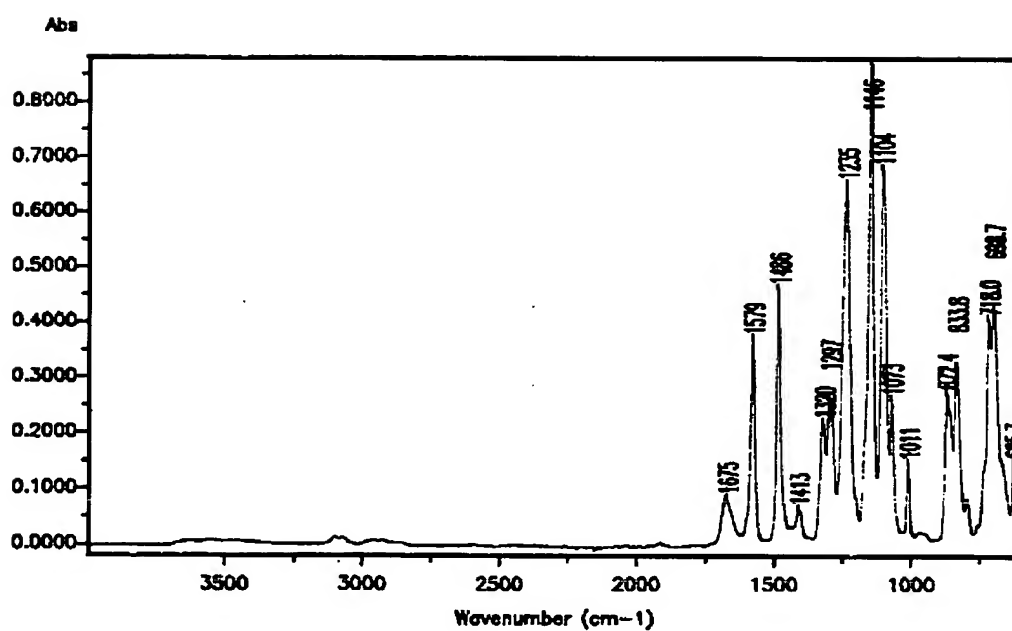
11/28/2006
dede
in
in
ad

[illegible][illegible]

【図4】



【図5】



[illegible]

フロントページの続き

Fターム(参考) 4D006 GA13 HA02 MA01 MA23 MA31
MA33 MA40 MB14 MC40X
MC62 MC63X NA04 NA16
NA17 NA18 PA01 PB09 PB54
PC46 PC47

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.